PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 124199/29 LAS	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/NZ2004/000267**	International filing date *(day/month/year)* 26 October 2004	Priority date *(day/month/year)* 24 October 2003
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 31/4184, 31/366, A61P 33/10, 33/14		
Applicant AGRESEARCH LIMITED et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 21 sheets, as follows:
      - [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand 20 June 2005	Date of completion of the report 12 October 2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NZ2004/000267

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages 1-6 as originally filed/furnished

pages* 7-22 & 26 (Abstract) received by this Authority on 17 June 2005 with letter of 17 June 2005

pages* received by this Authority on with the letter of

☒ the claims:

pages as originally filed/furnished

pages* as amended (together with any statement) under Article 19

pages* 23-25 received by this Authority on 17 June 2005 with the letter of 17 June 2005

pages* received by this Authority on with the letter of

☒ the drawings:

pages as originally filed/furnished

pages* 1/1 received by this Authority on 17 June 2005 with the letter of 17 June 2005

pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/figs

☐ the sequence listing (*specify*):

☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/figs

☐ the sequence listing (*specify*):

☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-24	YES
	Claims	NO
Inventive step (IS)	Claims 1-24	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-24	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

D1. AU 52162/96 A (694016) (Virbac Australia Pty. Ltd.) 21 November 1996
D2. Hennesy, D.R. "Modifying the formulation or delivery mechanism to increase the activity of anthelmintic compounds." Veterinary Parasitology, 1997 Nov; 72(3-4): 367-82;
D3. Awadzi K, Addy ET, Opoku NO, Plenge-Bonig A, Buttner DW. "The chemotherapy of onchocerciasis XX: ivermectin in combination with albendazole." Trop Med Parasitol. 1995 Dec; 46(4): 213-20.
D4. Grimshaw WT, Hong C, Webster R, Hunt KR. "Development of immunity to lungworm in vaccinated calves treated with an ivermectin sustained release bolus or an oxfendazole pulse release bolus at turnout." Vet Parasitol. 1996 Mar; 62(1-2): 119-24.
D5. Larsen JW, Vizard AL, Anderson N. "Production losses in Merino ewes and financial penalties caused by trichostrongylid infections during winter and spring." Aust Vet J. 1995 Feb; 72(2): 58-63
D6. Anderson N and Laby RH. "Activity against Ostertagia ostertagi of low doses of oxfendazole continuously released from intraruminal capsules in cattle." Aust Vet J. 1979 May; 55(5):244-6.

Novelty (N) and Inventive Step (IS):: Claims 1-24

The above citations, separately and in obvious combination, disclose mixtures of active anthelmintic agents, many being antibiotics, They include controlled release capsules but do not include intra-ruminal boluses of two or more different types of anthelmintics configured to release over 3 to 14 days, nor do any obvious combination of any of these citations. In the light of these citations, the invention is therefore considered to be novel and involve an inventive step.

Industrial Applicability (IA) Claims 1-24

Methods of treating animals and delivery devices for use in treating animals are industrially applicable.

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listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term 'comprised' or 'comprising' is used in relation to one or more steps in a method or process.

It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

According to one aspect of the present invention, there is provided a method of reducing parasites in animals characterised by the step of:

introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;

wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents each day for a period of between 3 and 14 days.

Preferably, the two or more anthelmintic compounds have different activities.

Preferably, the active agents are released at a substantially continuous rate.

Preferably the treatment will be formulated to effect a reduction in the parasite burden of an animal, and for ease of reference will be referred to as such throughout the specification. However, this should not be viewed as limiting, for the treatment may alternatively involve the administration of a number of

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different animal remedies.

For example, it is anticipated that the present invention could be used for treating an animal with an antibiotic, antiviral or antifungal treatment, particularly when attempting to achieve increased efficacy in the treatment of bacterial and viral infectious diseases.

Such treatments may be especially useful in the treatment of animal infections or animal parasites which have developed resistance standard drug treatments.

It is also anticipated that the present invention may find use in other animal treatments, such as the delivery of mineral and/or nutritional supplements, or so forth.

The term "animal" should be taken to encompass any ruminant animal in need of a reduction of parasites. The present invention is particularly suited to production animals, including but not limited to sheep, goats, cattle, deer and pigs.

For ease of reference throughout the present specification, the present invention will be described with reference to sheep, though this should not be seen as a limitation.

The term "parasite" should be taken to include endoparasites such as helminths, nematodes, cestodes, trematodes and combinations thereof; in addition to ectoparasites such as ticks, lice, flies, fleas and combinations thereof.

The term "anthelmintic" should be taken to mean compounds exhibiting activities selected from: nematocidal, flukicidal, trematocidal, cestocidal and/or ectoparasiticidal activities and combinations thereof.

The term "effective amount" should be taken to mean the level of anthelmintics necessary to effect a reduction in the level of parasites present in an animal, including a general increase in efficacy against resistant parasites, whilst minimising the undue selection of resistance to anthelmintics and the risk of toxicity to the animal.

In preferred embodiments of the present invention the anthelmintics used may be a macrocyclic lactone such as abamectin and a benzimidazole such as albendazole.

However, once again this should not be seen as limiting and other anthelmintics could be used such as organophosphates, salicylanilide/substituted phenols, tetramisoles or pyrimidine agents. Derivatives and variations of these compounds, and their specific anti-parasitic action are well known in the art and would be known to a skilled addressee.

In preferred embodiments the daily dose may be as close to the normal therapeutic (oral) dose as possible, while minimising toxicity risks. Therefore, for a given weight range of target animal, it is preferable to target the full dose to the lower end of that range.

Preferably, the daily dose delivered is substantially in the order of 3.0-5.0 mg/kg/day of albendazole and substantially 0.1-0.2 mg/kg/day of abamectin.

For example, for adult sheep in the range 50-80 kg it is preferable to deliver approximately 5 mg/kg of albendazole and approximately 0.2 mg/kg of abamectin to the 50 kg animal, which equates to approximately 3.125 mg/kg of albendazole and approximately 0.125 mg/kg of abamectin to the 80kg animal.

It should be appreciated these dosages are given by way of example only, and

should not be viewed as limiting. It is anticipated that the dose rates will vary with different anthelmintics and parasite resistance.

It is anticipated that daily delivery of the active agents over a period of three days will be the minimum required to cause an increase in efficacy over standard anthelmintic compositions.

In preferred embodiments of the present invention the active agents are released each day for a period of between 5 and 10 days.

The time period is also a balance between ensuring sufficient duration of exposure to ensure a significant increase in efficacy against resistant worms, whilst minimising the duration of exposure to avoid undue selection for resistance and the risks of toxicity of the anthelmintics to the animal.

It is anticipated that daily delivery of the active agents over a period of between 3 and 5 days will be the minimum required to ensure a substantial increase in efficacy over traditional anthelmintic preparations.

Most preferably, the active agents are released each day for a period of between 6 and 8 days.

Standard drenching programmes based on periods of weeks are easy to remember and calculate, making the final product user friendly. Further, such a time period allows for some variation in the delivery rates, whilst maintaining the efficacy of the treatment.

There are generally four forms of anthelmintic compositions currently available on the market, a single dose oral liquid drench, a single dose pour-on (dermal) liquid; a single dose liquid injection and sustained controlled release devices

which release a low level of anthelmintics from a solid matrix tablet encased in a plastic vehicle over an extended period of time (approximately 100 days).

Oral drenches deliver a one-off high dose of anthelmintic which kills approximately >95% of susceptible nematodes and provides the animal with a short period of time with a low worm burden.

Pour-on and injectable formulations release the drug in response to concentration gradients. This leads to a high initial concentration of drug within the animal, which subsequently declines. Such formulations are no more efficacious than oral formulations and have the disadvantage that the persistent declining concentrations of drug favour the development of resistance (Leathwick and Sutherland 2002 *Proceedings of the 32nd Seminar, The Society of Sheep and Beef Cattle Veterinarians, N.Z. Veterinary Association*, 115-127). Thus none of these formulations have been shown to have the potential to increase efficacy against resistant worms and/or slow the development of resistance.

It has previously been shown that repeated oral dosing (daily for five days) or continuous intraruminal infusion for a period of five days can increase the efficacy of albendazole treatment.

However, repetitive dosing of extensively-grazed animals with anthelmintics is not practicable. In large animals such as cattle and deer, oral drugs are also extremely difficult to administer, meaning the high majority of farmers use pour-on drenches. As the only combination products on the market are orals, there are very limited options for the use of combination products in these animals.

The available alternative to repetitive dosing is the provision of a controlled

release device. A number of studies have shown that efficacy against parasites can be increased by the provision of anthelmintics over an extended period of time, whilst requiring a lower daily level of dose than that required for a single dose.

Some controlled release devices (CRCs) are currently available that release between 1/5th and 1/10th the normal therapeutic dose (depending on animal liveweight) of either albendazole or ivermectin for 100 days. These devices act principally as prophylactics, maintaining parasites at low levels by preventing reinfection. However, such devices typically result in long withholding periods. Recent studies also do not support the view of increased efficacy of these devices over standard oral doses. Furthermore, the prolonged delivery of small doses of anthelmintics may actually select for resistance in the worm population.

Conventional controlled release devices are made from plastic and/or metal components which remain in the animal's rumen. Obviously there is a limit to the number of expired devices that can remain in an animal without consequences for the animal, and thus there is therefore a limit to how many CRCs can be given to an animal. Further, the component residues pose problems in freezing works when the offal is processed.

A second method of increasing efficacy against resistant worms is to combine different action families into a single product. The principle behind this approach is that worms resistant to one active will be killed by the second active. However, until recently the only commercially available anthelmintic products which used actives in combination against the same parasite species were oral combinations of benzimidazole and levamisole. As the anthelmintic classes have differing conditions of solubility and pH, it was difficult to formulate

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stable compositions of other actives.

If the anthelmintic composition does not kill resistant worms the numbers of such will build up in the population. Therefore, the efficacy of any anthelmintic product against resistant worms is a key feature in delaying the development of severe, production-limiting resistance.

In order to maximise the worm exposure to the anthelmintics, the applicants have developed a method of dosing animals which they have termed "maximum integral dose" and which combines high doses, extended duration and the combination of two or more anthelmintics into a single product, with the aim of achieving extremely high efficacy against parasites, including those resistant to normal doses of single actives.

The integral in mathematics is used to "find the area enclosed by a given curve" - in this case the area under the curve of worm exposure to anthelmintics.

To provide the maximum integral dose, the present invention may preferably utilise a controlled release device that delivers the equivalent of a high oral dose every day over a period of between 3 and 14 days, long enough to provide extremely high efficacy against parasites, but not long enough to build up resistance in the worm population.

The essence of the current invention is to produce a product which delivers enhanced efficacy against most resistant worm genotypes and therefore can be used to delay the emergence of resistance to the constituent actives.

As described above, high dose levels of one or more anthelmintics have previously only been delivered to animals as a single dose, due to the practical difficulties in repetitive dosing of extensively-grazed animals. Therefore, the

development of a method for delivering a maximum integral dose from a single delivery device has a number of significant advantages.

In preferred embodiments, the maximum integral dose will be delivered from a controlled release device which releases its payload over a period of between 3 and 14 days, which is retained in the rumen of an animal by virtue of its density, and which can release multiple anthelmintic actives at a constant, high rate.

By providing a dose rate that is sufficiently high for each active to ensure increased efficacy of each against parasites resistant to that class of drug, it is anticipated that the combination of extended duration with multiple actives will provide a very high efficacy product which will substantially delay the development of resistance.

By way of example, the inventors envisage a three active delivery device containing abamectin, albendazole and tricalbendazole. The first and second actives are nematocidal, while the latter two are flukicides. Such a composition would thus provide two double combinations in a single product containing three actives.

A major impediment to others developing short-acting controlled released devices has thus been the requirement for total degradation of the delivery mechanism. The delivery mechanism of the present invention may preferably be an intraruminal bolus which remains in place due to its density and which degrades completely, leaving no residue in the animal.

A number of intraruminal boluses are known in the art which could be adapted for use in the present invention, such as those described in WO 95/19763 and WO 01/87273.

In some embodiments, two active agents may be incorporated into the core of an intraruminal bolus, with a third active agent in the form of a tablet added to one end of the bolus. In this manner a triple combination of active agents can be delivered – the first as a result of the degradation of the tablet to give an initial dose, followed by the second and third active agents in combination released from the bolus over a period of between 3 and 14 days as described above.

Advantages of the present invention include:

1. High efficacy even in the face of moderate levels of resistance
2. Retardation of the further development of resistance
3. Complete degradation of the device, leaving no residue in the animal
4. Combination of otherwise incompatible actives in a solid matrix
5. Although a slow release device, it will not be sufficiently long-acting to pose a serious risk to developing resistance (as with the 100 day CRCs), or require a long withholding period.
6. Although a slow release device, it will deliver doses at or near the same rate as standard oral anthelmintics, significantly higher than other slow release devices, providing greater efficacy.
7. Ability to be used with large animal over 100kg, due to the ease of use resulting in a viable method of delivering combination products to cattle and deer.

It is thus anticipated that the delivery method may provide increased efficacy

against parasites not normally killed effectively by a single oral dose.

Oral albendazole has a label claim for efficacy against adult liver fluke but the level of efficacy appears variable and less than desirable (Coles & Stafford 2001. *Veterinary Record* 148: 723-724.). As in the case of nematodes, extended exposure of flukes to albendazole substantially increases efficacy (Kwan et al., 1988. *Journal of Controlled Release* 8: 31-38.).

Delivery of albendazole through the method of the present invention is anticipated to substantially increase efficacy against adult flukes. Further, while single dose albendazole appears to be ineffective against immature flukes, the latter may succumb to the longer-term administration of albendazole provided by the present invention.

The present invention further provides a composition, delivery means and methods of manufacture thereof, for delivering an effective amount of two or more active agents to animals over a period of between 3 and 14 days.

BRIEF DESCRIPTION OF DRAWINGS

Further aspects of the present invention will become apparent from the following description which is given by way of example only and with reference to the accompanying drawings in which:

Figure 1 Shows a typical dose/efficacy profile of a single dose of oral anthelmintics;

Figure 2 Shows a typical dose/efficacy profile of a typical slow release device, and

Figure 3 Shows a dose/efficacy profile of one preferred embodiment of the

present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

Figure 1 shows a typical dose/efficacy profile of a single, high dose of an oral anthelmintic. The oral dose removes greater than 95% of susceptible parasites and provides the animal with a period of time with a low parasite burden. However, this is followed by rapid re-infection.

Figure 2 shows a typical dose/efficacy profile of a current slow release device. These devices deliver a low level of a single anthelmintic over a long period of time (100 days). It acts as a prophylactic, maintaining parasites at low levels. This limits re-infection for about 100 days. Efficacy is similar to that provided by a single oral dose as shown by Figure 1, but can require a long withholding period after use.

Figure 3 shows a dose/efficacy profile of one preferred embodiment of the present invention. Parasites are removed at a very high efficacy, with some delayed onset of re-infection and delayed resistance. The extended short duration of exposure (between 3 and 14 days) requires only a short withholding period after use.

Proof of concept trials

Two aspects of the present invention which increase efficacy include A) the concept of extended duration and B) the combining of multiple actives; both independently contribute to increasing efficacy.

A) Extended duration.

Proof of concept for increasing efficacy with extended duration was

demonstrated in two different ways *i)* trials were conducted using repeated oral dosing to achieve extended duration thereby simulating a controlled release device and *ii)* Trials were conducted using prototype boluses releasing either albendazole or abamectin, hereinafter referred to as the "Magnum" bolus. Results are given below;

***i)* - Trials 1 & 2** – repeated oral dosing of albendazole and abamectin in lambs to extend duration of exposure.

Table 1a & b - Percentage efficacy of albendazole against albendazole resistant parasites in lambs – efficacy based on worm count.

1a – abomasa	% reduction in worm count	
Treatment	Trichostrongylus axei	Ostertagia Circumcincta
Alb - 5 mg/kg once	82.9	42.7
Alb - 5 mg/kg for 7 days	97.6	92.3
Alb – 3.75 mg/kg for 7 days	96.8	70.9
Alb – 2.5 mg/kg for 7 days	90.2	57.0
Alb – 1.75 mg/kg for 7 days	87.5	74.9

1b – small intestine	% reduction in worm count	
Treatment	Cooperia spp.	Nematodirus spp.
Alb - 5 mg/kg once	36.9	71.2
Alb - 5 mg/kg for 7 days	86.9	73.9
Alb – 3.75 mg/kg for 7 days	83.3	88.1
Alb – 2.5 mg/kg for 7 days	67.5	69.0
Alb – 1.75 mg/kg for 7 days	57.1	58.9

Table 2 - Percentage efficacy of abamectin against abamectin-resistant parasites in lambs – efficacy based on worm count.

Treatment	% reduction in worm count		
	Ostertagia circumcincta	Trichostrongylus colubriformis	Cooperia spp.
Aba – 0.2 mg/kg once	45.0	60.7	94.9
Aba – 0.18 mg/kg for 7 days	96.4	77.1	100.0
Aba – 0.113 mg/kg for 7 days	89.3	55.3	99.6
Aba – 0.07 mg/kg for 7 days	77.2	47.3	99.1
Moxidectin – 0.2 mg/kg once	76.3	72.5	99.1

These results showed that against a range of resistant parasites extending the

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duration of worm exposure to drug was always as good and often far superior to administering a single oral dose. In addition the varying dose rates showed that there was often a benefit in keeping the daily dose rate as high as possible, consistent with the concept of maximum integral dose as outlined in the present specification.

ii) **Trials 3 & 4 – Prototype Magnum boluses releasing albendazole in sheep and abamectin in cattle to achieve extended duration of exposure.**

<u>Table 3a & b - Percentage efficacy of oral albendazole and a prototype albendazole bolus against resistant parasites in adult ewes – efficacy based on worm count.</u>

3a – abomasa	% reduction in worm count		
Treatment	Ostertagia circumcincta	Trichostrongylus axei	Haemonchus Contortus
Albendazole – 5.0 mg/kg once	59.3	91.8	91.4
Albendazole bolus	86.9	92.5	98.7

3b – small intestine	% reduction in worm count
Treatment	Cooperia spp.
Albendazole – 5.0 mg/kg once	59.3
Albendazole bolus	86.9

<u>Table 4 – Percentage efficacy of pour-on abamectin, pour-on eprinomectin and a prototype Magnum bolus releasing abamectin against resistant Cooperia oncophora in cattle</u>

	% reduction in worm count
Treatment	Cooperia oncophora.
Abamectin pour-on	81.0
Eprinomectin pour-on	83.6
Abamectin bolus	97.4

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B) Combining actives.

Efficacy data for combining Benzimidazole and Levamisole actives against resistant parasites is reasonably common. Further, there is considerable evidence that these actives work independently and so it can be expected their combined efficacies will work in an additive manner (Anderson et al. 1991. *Australian Veterinary Journal* 68, 133-136.). Hence the expected efficacy of combining two or more actives can be calculated and compared with the measured value.

e.g. Farm 4 from Anderson et al, 1991

Efficacy of Levamisole	88%
Efficacy of albendazole	73%
Efficacy of Levamisole + albendazole	95%
Efficacy expected based on additive effects	97%

Data on combining the benzimidazole and macrocyclic lactone classes of actives (as is proposed in this specification) is harder to find, but some does exist for goats:

e.g. Data from Pomroy et al, 1992 (*New Zealand Veterinary Journal* 40, 76-78.)

Efficacy of ivermectin	27%
Efficacy of oxfendazole	82%
Efficacy of ivermectin + oxfendazole	97%
Efficacy expected based on additive effects	87%

This concept has again been tested for the present invention by constructing and testing for efficacy a Magnum bolus releasing 2 actives simultaneously. A prototype sheep bolus designed to release 5 mg/kg of albendazole and 0.18

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mg/kg abamectin in a 50 kg sheep was tested against two species of multiple drench resistant parasites. Trial lambs ranged in weight from 48 – 55.5 kg.

Table 5: Efficacy based on worm counts of a Magnum combination bolus (albendazole + abamectin), single standard oral doses of both albendazole and abamectin and moxidectin oral against multiple drug resistant *Ostertagia* and *Trichostrongylus* in sheep.

Treatment group	*Ostertagia circumcincta*	*Trichostrongylus colubriformis*
Magnum combination bolus	99.1	100
Albendazole oral + abamectin oral	38.9	94.0
Moxidectin-oral	59.9	90.6

Conclusion:

The results show a substantial increase in efficacy of the Magnum bolus over a combination of the same actives administered as two single oral doses. This supports the anticipated synergy which is the foundation of the present invention, i.e. extended delivery of each active gives increased efficacy, but by combining multiple actives an even greater step up in efficacy is achieved against resistant worms. This can also been seen in the comparison with moxidectin which although only a single active is recognised as the most potent single active product on the market.

C) Efficacy against flukes (Fasciola hepatica).

To test the efficacy of prolonged exposure to albendazole against liver fluke a trial was conducted using an albendazole only bolus in sheep. Sheep from a commercial farm with a previous history of fluke infections were screened by faecal egg count to identify animals carrying fluke infections.

These animals were then randomly allocated to one of two treatment groups on

the basis of these egg counts and one group was administered a magnum bolus releasing 5 mg/kg in a 50 kg animal. Twenty days after treatment all animals were slaughtered and livers recovered for fluke counts. Mean numbers of flukes recovered were 12.8 and 2.0 from the control and treated groups respectively, equating to an 84% reduction as a result of treatment.

Thus treatment with the Magnum bolus containing albendazole has resulted in a measureable efficacy against liver flukes.

Aspects of the present invention have been described by way of example only and it should be appreciated that modifications and additions may be made thereto without departing from the scope thereof as defined in the appended claims.

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WHAT WE CLAIM IS:

1. A method of reducing parasites in animals characterised by the step of:

   introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;

   wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents each day for a period of between 3 and 14 days.

2. A method as claimed in claim 1 wherein the said two or more anthelmintic compounds have different activities.

3. A method as claimed in claim 1 or claim 2 wherein the active agents are released at a substantially continuous rate.

4. A method as claimed in any one of the above claims wherein the said two or more active agents effect a reduction in the parasite burden of the animal.

5. A method as claimed in any one of the above claims wherein the said two or more active agents effect a reduction in the number of resistant parasites in the animal.

6. A method as claimed in any one of the above claims wherein said anthelmintic compounds are selected from those exhibiting activities selected from the group including: nematocidal, flukicidal, trematocidal, cestocidal, ectoparasiticidal activities and combinations thereof.

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7. A method as claimed in any one of the above claims wherein said anthelmintic compounds include a macrocyclic lactone.

8. A method as claimed in claim 7 wherein the macrocyclic lactone is abamectin.

9. A method as claimed in claim 8 wherein the abamectin is delivered at a dosage of substantially 0.1 – 0.2 mg/kg/day.

10. A method as claimed in any of the above claims wherein said anthelmintic compounds include a benzimidazole.

11. A method as claimed in claim 10 wherein the benzimidazole is albendazole.

12. A method as claimed in claim 11 wherein the albendazole is delivered at a dosage of substantially 3.0 - 5.0 mg/kg/day.

13. A method as claimed in any one of the above claims wherein said anthelmintic compounds include tricalbendazole.

14. A method as claimed in any one of the above claims wherein the animal is a sheep.

15. A method as claimed in any one of the above claims wherein active agents are released each day for a period of between 5 and 10 days.

16. A method as claimed in any one of the above claims wherein active agents are released each day for a period of between 6 and 8 days.

17. A method as claimed in any one of the above claims wherein the parasite is an endoparasite selected from the group including: helminths, nematodes, cestodes, trematodes, and combinations thereof.

18. A method as claimed in any one of claims 1 to 16 wherein the parasite is an ectoparasite selected from the group including: ticks, lice, flies, fleas, and combinations thereof.

19. A method as claimed in any of the above claims wherein the delivery device is a controlled release device.

20. A method as claimed in any one of the above claims wherein the delivery device delivers a maximum integral dose.

21. A delivery device for use in a method as claimed in any one of the above claims.

22. The use of two or more anthelmintic compounds of differing chemical groups in the manufacture of a delivery device as claimed in claim 21.

23. A method of treating animals substantially as described herein with reference to and as illustrated by the accompanying description and examples.

24. A delivery device substantially as described herein with reference to and as illustrated by the accompanying description and examples.

ABSTRACT

A method of treating animals characterised by the step of introducing to the animal a single delivery device containing two or more active agents, wherein the delivery device is configured to release an effective amount of active agents each day for a time period of between 3 and14 days.

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Figure 1

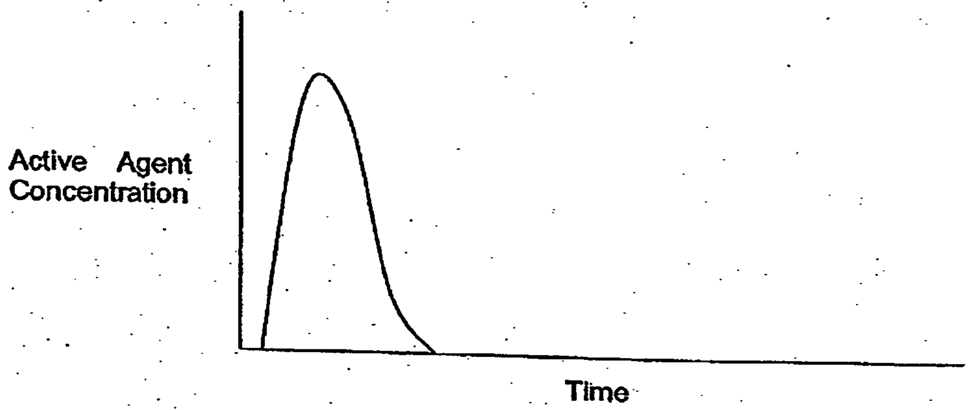


Figure 2

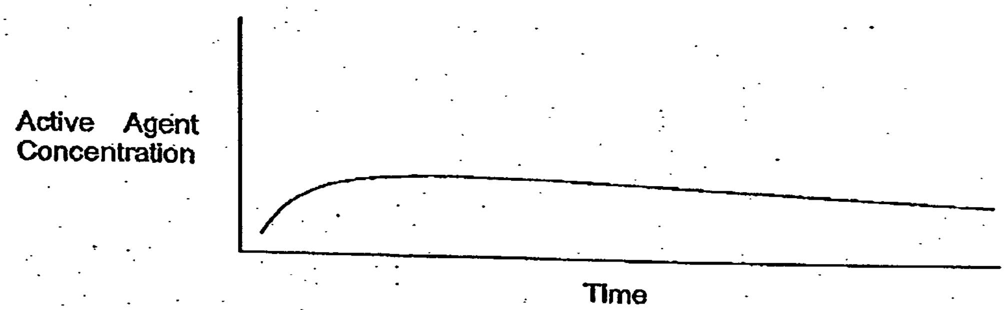
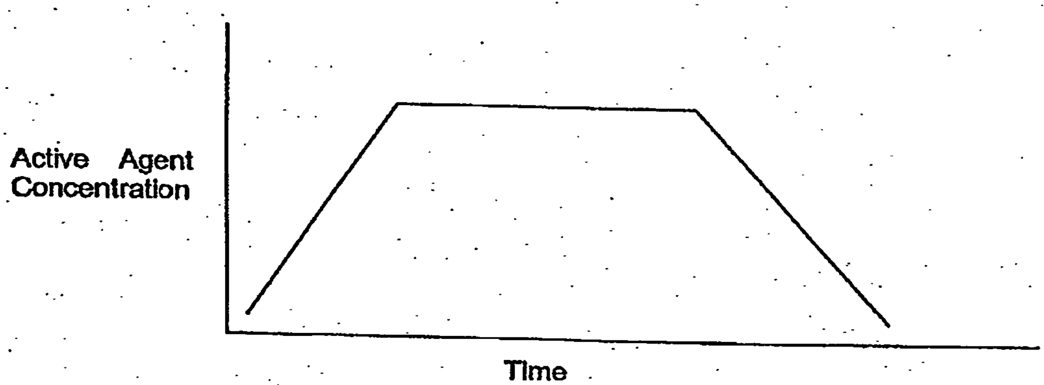


Figure 3



Amended Sheet
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